REMARKS

Comments regarding restriction requirement

Applicants reiterate that upon allowance of product claim 1, there should be rejoinder of "method of use" claims 12-13, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)." In addition, Applicants reiterate the impropriety of the "restriction requirement" between SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 and SEQ ID NO:7. Applicants expressly reserve the right to petition the restriction requirement if the full scope of the claims is not considered.

Objections to the title, abstract and specification

A new title is provided by the present amendment. The abstract has been reviewed and is believed to be descriptive of the claimed subject matter; hence, the abstract has not been revised. The specification has been amended to correct the typographical error regarding the description of "B15."

The Office Action states that "[t]here does not appear to be clear antecedent basis for the method steps of claims 3 and 6." Such, however, is not the case. The steps of claims 3 and 6 describe conventional methods for making polyclonal and monoclonal antibodies, respectively (although using the novel polypeptides of the invention so as to produce novel antibodies). The specification states that polyclonal and monoclonal antibodies of the invention "may be generated using methods that are well known in the art" (specification at page 29, lines 1-2). References describing such known methods for making antibodies are disclosed, for example, on pages 29-30 of the specification. In this regard, note the incorporation by reference of those documents at page 54, lines 1-2 of the specification. See also the description of polyclonal antibody production in Example X at pages 52-53 of the specification. Hence, proper support for the method steps of claims 3 and 6 is provided by the specification.

Rejection based on 35 U.S.C. §112, second paragraph

Claims 1-2 and 9-11 were rejected under 35 U.S.C. §112, second paragraph, for alleged

indefiniteness with respect to the recitation of "biologically active fragments." By the present amendment, the recitation of "biologically active" has been removed from the claims. Therefore, withdrawal of this rejection is requested.

Rejections based on 35 U.S.C. §112, first paragraph

1. Enablement Rejections

Claims 2, 5 and 8 have been rejected under 35 U.S.C. §112, first paragraph, allegedly for lack of an enabling disclosure with respect to the recitation of a "pharmaceutical composition." Claims 2, 5 and 8 have been amended so as to recite a "composition." Withdrawal of this rejection is therefore requested.

Claims 1 and 9-11 were rejected under 35 U.S.C. §112, first paragraph, allegedly for lacking an enabling disclosure with respect to variants and biologically active fragments of SEQ ID NO:3. This rejection is also traversed.

Claim 1 has been amended to remove recitation of "a biologically-active fragment" of a polypeptide of SEQ ID NO:3, thus rendering moot the rejection based on subsection (c) of claim 1.

The Office Action has asserted that the Specification provides insufficient guidance for one of skill in the art to obtain polypeptides that have 90% sequence identity to SEQ ID NO:3, *i.e.*, those embodiments within the scope of claim 1, part (b). The Action, however, exaggerates the difficulty in obtaining the recited polypeptides. The claims recite not only that the polypeptides have at least 90% sequence identity to SEQ ID NO:3, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences.

Given the information provided by SEQ ID NO:3 (the amino acid sequence of human NDS-2) and SEQ ID NO:4 (the polynucleotide sequence of human NDS-2), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence having at least 90% sequence identity to the full length of the sequence of SEQ ID NO:3." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was

filed and/or described throughout the Specification of the instant application. See, *e.g.*, page 37, lines 12-25; and Example VI at pages 50-51. Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:3. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. Moreover, once a candidate polypeptide is identified, its activity can be tested, *e.g.*, using the assay set forth in Example IX on page 52.

For at least the above reasons, withdrawal of this rejection is requested.

2. Written Description

Claims 1 and 9-11 are rejected under the first paragraph of 35 U.S.C. §112 for alleged lack of an adequate written description. According to the Office Action, the specification does not provide an adequate written description of "polypeptide variants" of SEQ ID NO:3. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate

description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:3.

SEQ ID NO:3 is specifically disclosed in the application (see, for example, page 2, lines 26-28). Polypeptide variants having at least 90% identity to SEQ ID NO:3 are described, for example, at page 5, lines 29 to page 6, line 6. In this regard, note that the claim language of "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of . . . SEQ ID NO:3" refers to a comparison to the full length of SEQ ID NO:3 since, by definition, SEQ ID NO:3 has 129 amino acids. Nevertheless, the present amendment clarifies the sequence identity comparison so that claim 1 now recites ". . . having at least 90% sequence identity to the full length of the sequence of . . . SEQ ID NO:3. Antibodies which specifically bind to the polypeptides recited in the claims are described, for example, at pages 29-30 of the Specification. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional

characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. An isolated antibody which specifically binds to a polypeptide comprising ...b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the full length of the sequence of ... SEQ ID NO:3, ...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to antibody proteins which specifically bind

subunits of NADH dehydrogenase related to the amino acid sequence of SEQ ID NO:3. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as subunits of NADH dehydrogenase and which have as little as 40% identity over at least 70 residues to SEQ ID NO:3. The "variant language" of the present claims recites, for example, "a naturally-occurring amino acid sequence having at least 90% sequence identity to the full length of the sequence of . . . SEQ ID NO:3 . . ." (note that SEQ ID NO:3 has 129 amino acid residues). This variation is far less than that of all potential subunits of NADH dehydrogenase related to SEQ ID NO:3, i.e., those subunits of NADH dehydrogenase having as little as 40% identity over at least 70 residues to SEQ ID NO:3.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of January 17, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:3 and SEQ ID NO:4, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins (and hence antibodies which specifically bind the proteins). In addition, the genus of antibodies able to bind to polypeptides as defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, withdrawal of this rejection is requested.

Rejections under 35 U.S.C. § 102 and § 103

Claims 1 and 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bentlage et al. (Biochimica Biophysica Acta, 1234:63-73, 1995). In addition, a § 103 rejection of claims 1-11 was applied over the combination of Walker et al (J. Mol. Biol., 226:1051-1072, 1992) in view of Bentlage et al and Ramakrishnan et al (U.S. Patent No. 5, 817,310). These rejections are traversed.

The present claims recite an antibody which **specifically binds** to a polypeptide comprising, *inter alia*, the amino acid sequence of SEQ ID NO:3, "90% variants" of SEQ ID NO:3, or immunogenic fragments of SEQ ID NO:3. Thus, the antibody encompassed by the claims must bind the recited polypeptides, and not other polypeptides.

Bentlage et al relates to a study of mitochondrial DNA-encoded and nuclear encoded subunits of human respiratory chain NADH dehydrogenase (Complex I) via the use of various antibodies. Those antibodies included polyclonal antibodies raised against the mtDNA-encoded ND4, ND5 and ND6 subunits. The ND4, ND5 and ND6 subunits have no apparent similarity to

SEQ ID NO:3 of the present invention, and none has been asserted by the Office Action.

Rather, the Action appears to rely on the description in Bentlage et al at page 65, section 2.4, of a polyclonal antibody raised against the bovine Complex I holo-enzyme. In this regard, the Office Action points to Figure 4a of Bentlage et al as showing "a polyclonal antibody that binds a 15kD protein of human Complex I" (Office Action at page 8). Bentlage et al, however, shows that this antibody does not specifically bind to a 15 kD protein. That is, the Western blot in panel a of Figure 4 shows that the antibody against bovine Complex I holo-enzyme binds to multiple subunits of the human complex. See also page 65, section 24 of Bentlage et al, which states that the antibodies against the bovine Complex I holo-enzyme "showed a reaction with approximately 10 subunits of Complex I preparation from bovine and human heart tissue." Clearly, then, Bentlage et al does not disclose an antibody which specifically binds SEQ ID NO:3.

Walker et al does not make up for the deficiencies of Bentlage et al. Walker et al describes a bovine B15 sequence of NADH:ubiquinone oxidoreductase which has some sequence similarity to SEQ ID NO:3. According to the Office Action, the sequence identity between the Walker protein and SEQ ID NO:3 is 75.8%. Hence, there are many amino acid residues of SEQ ID NO:3 not described by Walker et al which would have to be identified before an antibody could be produced which specifically binds SEQ ID NO:3. Neither Walker et al nor Bentlage et al provide any guidance on how to identify those amino acids.

Ramakrishnan et al describes various methods for producing antibodies, but has no information at all relating to SEQ ID NO:3. Hence, that document would not have guided one of skill in the art to the claimed subject matter.

For at least the above reasons, withdrawal of the § 102 and § 103 rejections is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Title beginning at line 2 of page 1 has been amended as follows:

ANTIBODIES TO [NOVEL] SUBUNITS OF NADH DEHYDROGENASE

Two consecutive paragraphs, beginning on page 12, line 26 to page 13, line 22 have been amended as follows:

In another embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:3, as shown in Fig. 2. NDS-2 is 129 amino acids in length. As shown in Fig 6, NDS-2 has chemical and structural homology with the bovine B15 subunit (GI 114). In particular, NDS-2 and B15 [15-kDa(IP)] share 74% identity. B15 is one of several nuclear encoded NADH-D subunits that lacks an N-terminal signal sequence, but is N-acetylated at an adjacent alanine or serine residue following removal of the initiator methionine. Both NDS-2 and B15 share the critical serine residue in position 2. As illustrated by Figs. 10A and 10B, NDS-2 and B15 have rather similar hydrophobicity plots. In particular NDS-2 and B15 share a peak of hydrophobicity between approximately residues 90 to 115 that is believed to be a membrane spanning alpha-helix. Northern analysis indicates that partial transcripts of the gene encoding NDS-1 are most abundant in cDNA libraries from cancerous tissues (26/81), particularly in prostate, brain, and bladder tumors, and in smooth muscle tissues (26/81). It is also notable in fetal and neonatal tissues, the brain and spinal cord, and in cells of the immune system.

In another embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:5, as shown in Fig. 3. NDS-3 is 106 amino acids in length. As shown in Fig 7, NDS-3 has chemical and structural homology with the bovine 15-kDa (IP) subunit (GI 224). In particular, NDS-3 and 15-kDa (IP) share 75% identity. The 15-kDa subunit is one of several subunits found in the iron-sulfur protein (IP) fraction during purification of NADH-D. The [15-kDa] 15-kDa (IP) subunit contains four cysteine residues, all of which are shared by NDS-3, that may form one of the iron-sulfur centers that functions in electron transport. As illustrated by Figs. 11A and 11B, NDS-3 and 15-kDa (IP) have rather similar hydrophobicity plots. Northern analysis indicates that partial transcripts of the gene encoding

NDS-3 are most abundant in cDNA libraries from cancerous tissues and immortalized cell lines (28/88), smooth muscle tissues (17/88), and in brain and neural tissues (10/88). They are also found in fetal, developing tissues and in tissues associated with inflammation and the immune response.

IN THE CLAIMS:

Claims 1, 2, 5, 6, 8 and 14 have been amended as follows:

1. **(Twice Amended)** An isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7,

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the full length of the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, and

c) [a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, and

d] an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, [SEQ ID NO:3,] SEQ ID NO:5, or SEQ ID NO:7.

2. **(Once Amended)** A [pharmaceutical] composition comprising the antibody of claim 1 in conjunction with a suitable pharmaceutical carrier.

5. **(Once Amended)** A [pharmaceutical] composition comprising the antibody of claim 4 in conjunction with a suitable pharmaceutical carrier.

6. **(Once Amended)** A method of making a monoclonal antibody with the specificity of the antibody of claim 1 comprising:

a) immunizing an animal with the polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ

ID NO:5, or SEQ ID NO:7, or an antigenically-effective fragment thereof under conditions to elicit an antibody response;

b) isolating antibody producing cells from the animal;

c) fusing the antibody producing cells with immortalized cells in culture to form monoclonal antibody-producing hybridoma cells;

d) culturing the hybridoma cells; and

e) isolating from the culture monoclonal [antibodies] antibody which binds specifically to the polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

8. **(Once Amended)** A [pharmaceutical] composition comprising the antibody of claim 7 in conjunction with a suitable pharmaceutical carrier.

14. **(Once Amended)** An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

a) a polypeptide having an amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7,

b) a naturally-occurring polypeptide having an amino acid sequence at least 90% identical to the full length of the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, and

c) [a biologically-active fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, and

d)] an immunogenic fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, [SEQ ID NO:3,] SEQ ID NO:5, or SEQ ID NO:7.